**UNITED STATES PATENT AND TRADEMARK OFFICE**

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**BEFORE THE PATENT TRIAL AND APPEAL BOARD**

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COHERUS BIOSCIENCES, INC.,
Petitioner,

v.

HOFFMANN-LA ROCHE INC.,
Patent Owner

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Case IPR2017-02066
Patent No. 8,063,182

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# PATENT OWNER'S PRELIMINARY RESPONSE

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## I. INTRODUCTION

Seeking to subvert ongoing litigation under the biosimilars statute by proffering theories the Board twice has found unpersuasive, Petitioner asks the Board to find the claims of U.S. Patent No. 8,063,182 ("the '182 patent") obvious over prior art describing non-TNFR fusion proteins having no functional relevance to TNF or treating inflammatory diseases. The Board need not revisit these theories again.

The '182 patent generally claims a fusion protein made from parts of two unrelated proteins – a TNF-binding portion of the p75 tumor necrosis factor receptor ("p75 TNFR") and a defined portion of a human IgG immunoglobulin heavy chain (*i.e.*, "all of the domains of the constant region of a human IgG immunoglobulin heavy chain other than the first domain…"). The commercial embodiment of the '182 patent and its sister, U.S. Patent No. 8,163,522,[1] is etanercept, a novel protein having unexpected properties that have made it a potent and effective anti-inflammatory.

[1] Both patents are asserted in ongoing litigation with a different biosimilar manufacturer (Sandoz) pursuant to the Biologics Price Competition and Innovation Act (BPCIA). *Immunex Corp. v. Sandoz Inc.*, No. 2:16-cv-01118 (D.N.J. Feb. 26, 2016).

Etanercept is ground-breaking. The active ingredient of Enbrel®, the first FDA-approved human therapeutic fusion protein, has improved the lives of countless patients afflicted with debilitating inflammatory diseases such as rheumatoid arthritis (RA). Etanercept was the first therapeutic to do more than merely treat the symptoms of RA – by capturing tumor necrosis factor ("TNF") (an inflammation-causing cytokine), it can slow and sometimes even stop the severe joint damage that are RA's hallmark. Etanercept is unquestionably successful – immediately after its launch, Enbrel® became physicians' leading choice for treating RA, and it continues to be widely prescribed for RA despite the launch of other biological products targeting TNF.

Etanercept's success is attributable to several of its unexpected properties tied to its unique structure. Etanercept binds TNF with much greater affinity and neutralizes TNF activity 1000-fold more effectively than p75 TNFR – properties that make it uniquely well-suited for treating diseases caused by uncontrolled inflammation. Etanercept also does not aggregate when it binds TNF ligands in solution, an unexpected result given that other bivalent proteins like anti-TNF antibodies do. And despite incorporating a portion of the IgG1 constant region, it does not cause meaningful antibody-dependent cell-mediated cytotoxicity (ADCC) and complement dependent cytotoxicity (CDC) – a surprising result given that IgG1 antibodies are the most potent inducer of those activities. Humira®) and

Remicade® – which contain the high affinity IgG1 antibodies adalimumab and infliximab, respectively – cause such effects.

Given etanercept's therapeutic benefits and overwhelming clinical success, many companies, including Petitioner, are pursuing commercial strategies to copy it. This Petitioner, however, views challenging etanercept's patents in this forum – rather than under the BPCIA – to provide it a commercial advantage.[2] Not only is this improper under the BPCIA's design of the BPCIA, it is entirely unwarranted here, given that the Petition falls far short of the statutory requirement for demonstrating "there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition."[3]

## II. SUMMARY OF RESPONSE

The Petition presents a textbook example of a petition that should be denied under either or both of 35 U.S.C. §§ 325(d) and 314(a). It not only advances obviousness theories substantively indistinguishable from those the Board has now

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[2] Ex. 2029 (Coherus Press Release) at 2 ("[C]hallenging these patents in IPR aligns with our decision to refocus the priorities of our etanercept biosimilar program, CHS-0214, on the potential U.S. opportunity...."). All citations refer to the Exhibits' native page numbers.

[3] 35 U.S.C. § 314(a).

twice rejected, but frames its arguments largely as a reply to the Board's past findings.

Petitioner's grounds rely on prior art teachings exhaustively considered during original examination and an earlier request for *inter partes* review.[4] Both rely on the Smith patent (Ex. 1004) in combination with references describing the same fusion proteins the Board previously considered.[5] Even Petitioner's supposed motivations are the same: a desire for "practical yields," half-life improvements, enhanced binding, and ease of purification. Permitting serial challenges under immaterially different obviousness theories based on the same or substantially the same teachings in the prior art is flatly contrary to the policies underlying §§ 325(d) and 314(a), and warrants non-institution.

During examination, the Examiner rejected the recited fusion proteins as obvious over prior art showing "hybrid" proteins combining unrelated receptors with portions of immunoglobulin chains. The Board reversed those rejections,

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[4] IPR2015-01792 ("CFAD-IPR") (concerning the '522 patent).

[5] Zettlmeissl (Ex. 1005) and Watson (Ex. 1003).

based on, *inter alia*, evidence of objective indicia of non-obviousness, including some of etanercept's unexpected properties.[6]

In 2015, the Board declined to institute *inter partes* review of the related '522 patent based on an obviousness rationale substantively indistinguishable from those addressed during examination and presented here, explaining:

> [T]he generalized guidance in Seed and Capon [teaching non-TNFR "hybrid" proteins] would not have led one of ordinary skill in the art to produce a p75 TNFR-based fusion protein having a structure that corresponds to the expression products of the challenged claims or the protein encoded by the polynucleotides described in the challenged claims.[7]

The Board rejected the proposition – which this Petitioner now repeats – that a need to achieve "practical yields" of a TNFR-based fusion protein would have led an Ordinary Artisan to "select the hinge-$C_H2$-$C_H3$ constant region of the immunoglobulin."[8]

The Board also found etanercept's unexpected properties – identified during examination of the '182 patent – to support non-obviousness. It rejected CFAD's

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6 *See* Ex. 1021 (11/22/2010 Decision) at 7 ("Appellants' evidence of unexpected results is convincing to rebut the Examiner's obviousness rejection.").

7 *See* Ex. 1010 (CFAD-Dec.) at 15.

8 *Id.* at 16.

assertion this evidence had no nexus to the claims, stating "[t]he evidence of unexpected results is commensurate in scope with the claims," and faulted CFAD for not addressing it, observing "[t]he Petition, moreover, should have addressed the evidence of unexpected results as part of Petitioner's showing of a reasonable likelihood of success."[9]

Neither of the grounds in this Petition can be meaningfully differentiated from those the Board has repeatedly rejected. Each employs hindsight, and each rests on an inaccurate portrayal of both the prior art's teachings and the Ordinary Artisan's beliefs in August 1990. And, as in the CFAD-IPR, each ignores compelling objective indicia of non-obviousness.

Petitioner's first ground ("Ground One") portrays the claimed p75 TNFR fusion protein as an obvious variant of Watson's fusion protein. That protein, however, was based on the murine peripheral lymph node homing receptor ("pln-HR"), an "adhesion molecule" that facilitates the physical migration of lymphocytes through lymph nodes, and was used "as a histochemical reagent for the staining of pln HEV" and "analyzing the distribution of HR ligand(s) in normal as well as in inflammatory states."[10]

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9 *Id.* at 18.

10 Watson at 2221.

Aside from not providing any insights relevant to therapeutically targeting a soluble cytokine like TNF, Watson's pln-HR fusion protein did not use "the identical portion of the IgG heavy chain as claimed in the '522 patent" as Petitioner claims.[11] It used a truncated IgG1 hinge in combination with the $C_H2$ and $C_H3$ domains, while the claims require the complete hinge with those domains (*i.e.*, "all of the domains of the constant region of a human IgG immunoglobulin heavy chain other than the first domain of said constant region"). Consequently, following Petitioner's "straightforward application of Watson's method to the 75-kDa TNFR" does not yield the fusion proteins of the claims, a deficiency Petitioner neither acknowledges nor resolves.[12]

Petitioner's second ground ("Ground Two") is likewise hindsight-based and incorrectly portrays its cited references' teachings. This ground is anchored in Smith, which the Board has twice found insufficient to render the claimed fusion proteins obvious.

Smith described a tetrameric p75 TNFR-based "chimeric" antibody that replaces only the variable regions in one or both of the heavy and light chains with

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11 Pet. at 5 (original emphasis).

12 *Id.* at 31.

"TNF-R" but otherwise retains "unmodified constant region domains."[13] As Petitioner admits, the '182 patent claims expressly exclude the $C_H1$ domain and the light chain constant domain.[14]

To escape Smith's literal teachings, Petitioner simply invents a problem – suboptimal expression – and asserts this would have led an Ordinary Artisan to a "well-known, optimized method of preparing fusion proteins" allegedly disclosed in Watson and another reference, Zettlmeissl.[15]

But that supposed motivation, conspicuously unsupported by expert testimony, is the same "practical yields" motivation the Board found unpersuasive in the CFAD-IPR:

> Such motivation ['for practical yields'] does not provide a reason for one of skill in the art to select the hinge-$C_H2$-$C_H3$ constant region of the immunoglobulin from the teachings of Seed or Capon to combine with Smith's TNF-R gene. [16]

Worse, Petitioner's arguments rest on inaccurate depictions of the secondary references. As it did with Watson's fusion protein, Petitioner incorrectly portrays

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13 Smith at 10:53–57.

14 Pet. at 1.

15 Pet. at 26.

16 Ex. 1010 at 16.

Zettlmeissl's fusion proteins, stating they consist of a "receptor [that] is attached directly to the hinge-CH2-CH3 region of an IgG antibody's heavy chain."[17] Zettlmeissl's proteins actually have a third component, a synthetic "5-amino-acid linker sequence," interposed between each protein's CD4 and IgG1 portions, a distinction Petitioner largely ignores.[18] Petitioner also claims these proteins do not exhibit CDC, ignoring contrary indications in Zettlmeissl and a contemporaneous paper from the same researchers showing they "unequivocally" do. [19]

Petitioner's hindsight-driven theories, coupled with its inaccurate portrayal of the prior art, fall far short of the standards required for institution.

Independently, the Board should deny the Petition because substantial evidence of objective indicia supports the non-obviousness of the claims. Importantly, Petitioner nowhere disputes the Board's past findings of a nexus between etanercept and the claims – that its unexpected properties are

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17 *E.g.*, Pet. at 4 (emphasis added); *id.* at 10 (claiming Zettlmeissl "discloses fusion proteins in which the CD4 receptor is fused to the hinge region of an IgG antibody.")

18 Zettlmeissl at 348.

19 Ex. 2020 (Gregersen) at 41.

"commensurate in scope with the claims."[20] Then, inexplicably, Petitioner ignores several objective indicia associated with etanercept of which it is certainly aware: (i) substantial commercial success, (ii) addressing a long-felt need for an effective RA treatment, and (iii) copying by Petitioner and others. Petitioner's sole challenge is to the unexpected results of etanercept. But that – like much of the petition – rests on an incorrect description of both the science and the Ordinary Artisan's knowledge and expectations in August 1990.

The Board should decline to institute *inter partes* review.

## III. THE '182 PATENT

Petitioner filed two petitions – one against the '182 composition patent and the other against its sister '522 method patent. The two petitions advance nearly identical obviousness grounds, relying on the same references and arguments and using almost the same language. Petitioner also treats each patent's prosecution histories as establishing a common prosecution history applicable to both patents.[21]

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[20] Ex. 1010 at 18; *see also* Ex. 1021 at 7.

[21] *See* IPR2017-01916, Paper 1 at 16 ("Prosecution of the '522 Patent Tracked that of the '182 Patent").

### A. The Patent Disclosure

The '182 patent describes fusion proteins made from portions of two different proteins: (i) some or all of the extracellular region of either the p55 or the p75 tumor necrosis factor receptor ("p55 TNFR" and "p75 TNFR")[22] and (ii) a human immunoglobulin heavy chain lacking the $C_H1$ domain. As it explains:

> The invention is also concerned with DNA sequences which comprise a combination of two partial DNA sequences, with one of the partial sequences coding for those soluble fragments of non-soluble proteins which bind TNF (see above) and the other partial sequence coding for all domains other than the first domain of the constant region of the heavy chain of human immunoglobulins such as IgG, IgA, IgM or IgE, in particular $IgG_1$ or $IgG_3$ subtypes.[23]

The specification portrays the invention as "TNF binding proteins" ("TNF-BP") including "proteins which consist of a soluble fragment of non-soluble TNF-BP and an immunoglobulin fragment, *i.e.*, all domains except the first of the constant region of the heavy chain."[24] It explains these fusion proteins can be

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[22] '182 patent, 2:47–51, 2:60–62, Fig. 1, Fig. 4. *See also id*. at 5:25–53 (indicating sequence deposited with ATCC).

[23] '182 patent at 5:54–61.

[24] *Id.* at 8:56–60.

made using, among other things, vectors "pDC4-Hγ1 [sic] (DSM 5314)" and "pCD4-Hγ3 (DSM 5523)."[25] Example 11 illustrates production of one such TNF-BP example using the p55 TNFR, in which the TNFR's extracellular region was attached directly to the hinge-$C_H2$-$C_H3$ sequence of an IgG3 heavy chain.[26] The specification also describes pharmaceutical preparations and uses for these TNF-BP's.[27]

### B. Claim Construction

Claims 1, 13, 18, 26, and 30 are independent and each claims a fusion protein that "specifically binds TNF" and is made up of a "soluble fragment" of the p75 "TNF receptor" (such as the "extracellular region"), which itself "specifically binds human TNF," combined with an explicitly defined portion of an IgG immunoglobulin: "all of the domains of the constant region of a human immunoglobulin [IgG/IgG1] heavy chain other than the first domain of said constant region."

In the CFAD-IPR, the Board interpreted the terms "TNF receptor," "all of the domains of the constant region of a human [IgG/ IgG1] immunoglobulin heavy

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25 *Id.* at 8:56–9:8.

26 *Id.* at 20:46–21:10; Ex. 2001 (Croft-Decl.) ¶¶46–47, 59.

27 *Id.* at 6:26–35.

chain other than the first domain of said constant region" and "about."[28] Petitioner and its expert have accepted those constructions without comment.[29]

Patent Owner agrees with the Board's prior constructions, but believes a brief explanation is warranted due to significant errors in the Petition and Dr. Burton's declaration – both incorrectly claim that: (i) the IgG components of the fusion proteins in Watson and Zettlmeissl are "identical" to the claimed fusion proteins[30] (and thus necessarily to each other) and (ii) that Zettlmeissl "discloses

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28 *Id.* at 4–7.

29 Pet. at 19–20; Ex. 1002 (Burton-Decl.) ¶¶33–34.

30 *See, e.g.*, Pet. at 5 ("Watson and Zettlmeissl used different receptors in their fusion proteins, but both reported optimal results by employing the identical portion of the IgG heavy chain as claimed in the '182 patent."); *id.* at 18 ("…Watson and Zettlmeissl expressly directed the POSA to choose exactly the immunoglobulin fragment claimed in the '182 patent – the 'hinge-CH2-CH3' region of a human IgG heavy chain."); *id.* at 30 ("Watson's fusion protein is identical to the fusion protein of the '182 patent claims, except that the receptor protein is different."). *See also* Burton-Decl. ¶145 ("Watson's fusion protein is identical to the fusion protein of the '182 patent claims, except that Watson's receptor is the extracellular domain of pln HR…."); *id*. ¶164 ("Zettlmeissl created

fusion proteins in which the CD4 receptor is fused to the hinge region of an IgG antibody."[31]

Both assertions are demonstrably false – the Watson fusion protein uses a truncated human IgG1 heavy chain hinge-$C_H2$-$C_H3$ sequence that omits the first five residues of the exon-encoded hinge domain, while the Zettlmeissl fusion proteins interpose an artificial linker sequence between the IgG1 and CD4 receptor sequences. A simple alignment reveals both errors:[32]

| | | | |
|---|---|---|---|
| IgG1 | [IgG1-CH1] | EPKSCDKTHTCPPCP | APELLGGPSVFLF… |
| | CH1 | HINGE | CH2 |
| Watson | [mHRLEC] | -----DKTHTCPPCP | APELLGGPSVFLF… |
| | pln-HR | HINGE | CH2 |
| Zettlmeissl | [CD4]-**HADPE** | EPKSCDKTHTCPPCP | APELLGGPSVFLF… |
| | CD4+Linker | HINGE | CH2 |

Petitioner glosses over these errors. But a precise identification of the differences between the prior art fusion proteins and the claims is factual prerequisite of an obviousness assessment.

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fusion protein constructs wherein CD4 was joined directly to CH1, the hinge region, or CH2 of the heavy chain.").

31 Pet. at 10; *see also id.* at 4.

32 Croft-Decl. ¶¶119–121, 150–161; Ex. 1050 at Fig. 4; Zettlmeissl at Fig. 1.

The Board should maintain its prior construction – that the IgG/IgG1 element of the claims requires use of the "'-hinge-$C_H$2-$C_H$3' region of a human IgG/IgG1 immunoglobulin heavy chain" – which means, under the plain and ordinary meaning of the claim language, and consistent with the specification and prosecution history, that the claims require use of the entire hinge-$C_H$2-$C_H$3 region of the IgG/IgG1 heavy chain, not a truncated portion of it.

First, the claims expressly require use of all of a human IgG or IgG1 heavy chain constant region except for the first domain. By their terms, the claims thus require use of the entire amino acid sequence of the specified heavy chain except for the sequence within the first (*i.e.*, $C_H$1) domain.

The plain and ordinary meaning of "$C_H$1 domain" is the amino acid sequence encoded by the "$C_H$1 domain" exon in the four IgG sub-type genes. As Dr. Elvin Kabat explained in his seminal work on immunoglobulin sequences:

> The $C_H$ and hinge domains conform to the findings of Sakano et al. (172), who defined each domain precisely by sequencing the coding and intervening nucleotide sequences bordering each domain.
>
> The extensive nucleotide sequence data on exons for the constant regions of heavy chains have provided exact boundaries for $C_H$1, hinge, $C_H$2, $C_H$3, and $C_H$4.[33]

[33] Ex. 2012 (Kabat) at xix. *See also* Ex. 2014 (Sakano) at Fig. 4.

Ellison (Ex. 1050) likewise describes the amino sequence of the $C_H1$ domain (and of the other domains) of human IgG heavy chains as being encoded by the $C_H1$, hinge, $C_H2$ and $C_H3$ exons.[34]

Ellison also compared the boundaries of the $C_H1$-hinge-$C_H2$ domains of three IgG isotype heavy chains as defined by their exons (below), illustrating each begins with a glutamic acid (E) and ends with a proline (P):

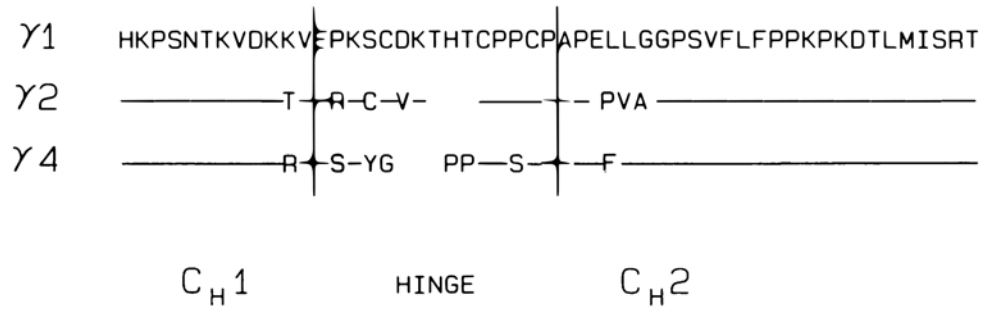
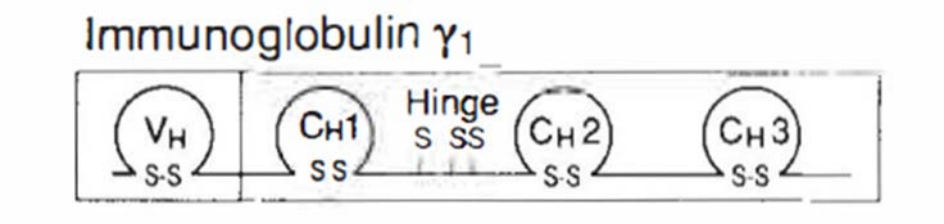



**Figure 4. Comparison of amino acid residues in the hinge area of three $C_\gamma$ polypeptides. Vertical lines separate the hinge residues from those contiguous amino acids which are encoded in the $C_H1$ and $C_H2$ exons. Amino acids are listed in the one-letter code. Solid lines represent identity of the γ2 and γ4 sequences to the γ1 sequence. The $C_H2$ domain of the $C_{\gamma 2}$ sequence contains one less amino acid than is found in the other genes.**

[34] Ex. 1050 at 4072 ($C_H1$, hinge, $C_H2$ and $C_H3$ sequences in IgG1 polypeptide "are encoded in individual exons that are separated from one another by introns, the largest one lying between the CH1 and hinge exons."); Croft-Decl. ¶¶62–64. Dr. Burton cites Ellison as proof that the DNA sequences encoding the various IgG heavy chains were "well known." Burton-Decl. ¶129.

Notably, Ellison shows the IgG1 hinge containing three cysteine residues. Capon (Ex. 1032) ("Capon") (which Petitioner and its expert cite[35]) likewise indicates the "hinge region of each [IgG1-based] immunoadhesin contains three cysteine residues, one normally involved in disulphide bonding to light chain, the other two in the intermolecular disulfide bonds between the two heavy chains in IgG."[36] Capon also shows in Fig. 1 the IgG1 heavy chain having three disulfide bonding sites in the hinge domain downstream from the $C_H1$ domain:




The specification and prosecution history are consistent with this understanding of what the hinge-$C_H2$-$C_H3$ of IgG and IgG1 heavy chains constitutes. For example, the specification describes examples of "especially suitable" vectors for expressing TNFR fusion proteins that contain sequences encoding the complete, exon-encoded hinge-$C_H2$-$C_H3$ sequence of an IgG1 or

35 *E.g.*, Pet. at 36–37; Burton-Decl. ¶¶63–69.

36 Ex. 1032 at 526 (emphasis added).

IgG3 heavy chain (*i.e.*, sequences omitting only the amino acids in the exon-defined $C_H1$ domain).[37]

Likewise, during prosecution, Patent Owner distinguished the claims from other fusion proteins having "only a portion of a hinge domain," stating "[b]oth are missing the first several amino acids of this domain…"[38] Patent Owner also noted during the CFAD-IPR that the claims "were drafted to exclude other p75 TNFR/IgG fusion proteins (such as Delta 57 and Protein 3.5D) that contained only a portion of the hinge domain and did not display the unexpected properties."[39]

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[37] *E.g.*, '182 patent at 8:56–9:8 (describing pCD4-Hγ1 and pCD4-Hγ3 vectors for use in "expression of proteins which consist of a soluble fragment of non-soluble TNF-BP and an immunoglobulin fragment, *i.e.*, all domains except the first of the constant region of the heavy chain" and citing to EP Appl. No. 90107393.2, which confirms that these vectors were made with "exons" encoding the full hinge, $C_H2$, and $C_H3$ domains); Ex. 1011 ('393 Application); Croft-Decl. ¶¶40–45, 59.

[38] Ex. 2110 (3/15/2011 Response) at 35.

[39] *See* Ex. 1008 (CFAD-POPR) at 40 (emphasis added); *id*. at 47 (Capon-964 preferred embodiments use "'the entire heavy chain constant region' (including CH1)" or "part but not all of the hinge domain").

Consequently, the Board's prior interpretation of the meaning of the IgG element of the claims as requiring use of the hinge-$C_H2$-$C_H3$ portion of the IgG or IgG1 heavy chain should be maintained.[40]

### C. Etanercept Is a Commercial Embodiment of the Inventions

Etanercept, Enbrel®'s active ingredient, is a fusion protein consisting of the extracellular region of p75 TNFR fused directly to the hinge-$C_H2$-$C_H3$ region of a human IgG1 heavy chain.[41] It is produced by CHO cells transfected with DNA encoding the fusion protein.[42]

Etanercept assembles as a homodimer, with the IgG hinge's three cysteine residues forming disulfide bonds with complementary cysteine residues in the hinge of its dimeric partner, yielding the structure depicted below:[43]

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[40] If the Board believes a clarification of its prior construction is warranted, it could add the words "complete, exon-encoded" before the phrase "-hinge-CH2-CH3" in its prior construction. Doing so would yield the meaning compelled by the claim language, the patent disclosure and the prosecution history.

[41] Ex. 2004 (Enbrel® Label) § 11.

[42] *Id.*

[43] Ex. 2007 (Molta) at 32, Fig. 4.1.

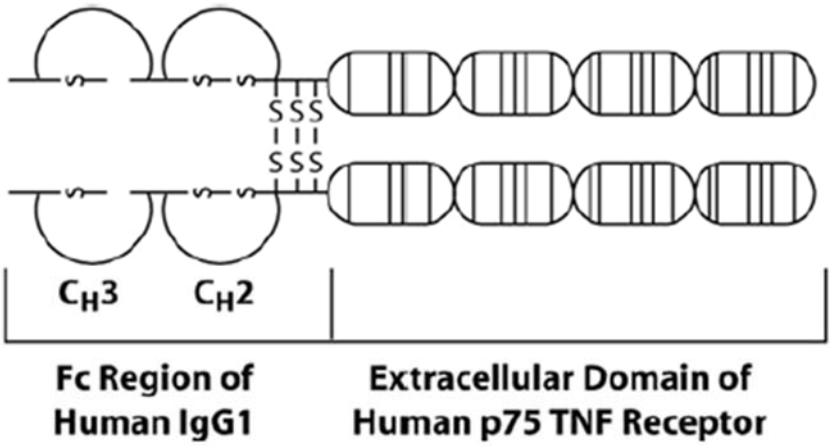


**Fig. 4.1.** Chemical structure of etanercept. *IgG1* immunoglobin G1, *TNF* tumor necrosis factor

Etanercept thus embodies the '182 patent's claims,[44] which Petitioner nowhere disputes.

## IV. THE BOARD SHOULD EXERCISE ITS DISCRETION UNDER § 325(d) AND/OR § 314(a) AND NOT INSTITUTE TRIAL

Under § 325(d), "[i]n determining whether to institute or order a proceeding," including an IPR, the Board "may take into account whether, and reject the petition or request because, the same or substantially the same prior art or arguments previously were presented to the Office." The Board has also relied on § 314(a) to decline to institute trial when a petition advances substantially the same

[44] Croft-Decl. ¶¶48–53.

challenge that had been earlier considered by the Board or the Office.[45] And the Board has found that § 314(a) applies to cases "in which a different petitioner filed a petition challenging a patent that had been challenged already by previous petitions."[46]

Under either standard, the Board should exercise its discretion and decline to institute trial. The Board has considered not only the substantive teachings of the prior art in both of Petitioner's grounds, but also the specific obviousness rationales Petitioner advances based on them.

### A. The Board Has Twice Found the Fusion Protein of the Claims Non-Obvious Over Unrelated Fusion Proteins

#### 1. Examination of the '182 and '522 Patents

During examination of U.S. Appl. No. 08/444,790 ("the '790 application") (the '182 patent), the Examiner imposed written description and obviousness rejections, and for the latter, cited Dembic (Ex. 1018) as teaching the "full-length

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[45] *See, e.g.*, *Gen. Plastic Indus. Co., Ltd., v. Canon Kabushiki Kaisha*, IPR2016-01357, Paper 19, at 16–17 (PTAB Sept. 6, 2017) (declining to institute because petition fosters "abuse of the review process by repeated attacks on patents.")

[46] *Netapp, Inc. v. Realtime Data, LLC*, IPR2017-01354, Paper 16, at 8–9 (PTAB Nov. 14, 2017).

amino acid sequence of" p75 TNFR and U.S. Patent No. 5,116,964 ("Capon-964") (Ex. 1019) as teaching attachment of a "truncated murine lymphocyte homing receptor (MHLR) to the Fc region of human IgG1."[47]

Patent Owner appealed, explaining an Ordinary Artisan "would have been discouraged from fusing an anti-inflammatory agent, such as soluble fragments of p75 TNFR, to the pro-inflammatory constant region of an immunoglobulin heavy chain."[48] Patent Owner also cited evidence of unexpected results observed with etanercept, including "reduced pro-inflammatory effector functions," "lack of aggregating ability," "unexpected thousand-fold increased potency in TNF neutralization activity," and "unexpectedly increased binding affinity and kinetic stability."[49]

The Board reversed the Examiner's rejections. It found "the written description supports the pending claim scope." It observed the Examiner did not dispute the unexpected results of etanercept, and found (as it did during original

47 Ex. 2031 (2/23/2007 Final Rejection) at 14.

48 Ex. 1006 (2/28/2008 Appeal Br.) at 42.

49 *Id.* at 48–55.

examination) that evidence "convincing to rebut the Examiner's obviousness rejection."[50]

Nonetheless, the Examiner again rejected the claims as obvious, replacing Dembic with Smith, and using a continuation of Capon-964 (U.S. Patent No. 5,428,130 (Ex. 1022, "Capon-130"), which was portrayed as disclosing a "murine lymphocyte homing receptor (MHLR) extracellular domain" "fused to the Fc region of human IgG1"[51] and teaching a "variety of uses" for its fusion proteins, including "prolonging in vivo plasma half-life, facilitating purification."[52]

Patent Owner, citing the Board's decision, argued the rejections were improper, explaining, *inter alia*, that "[t]he ordinary skilled artisan following the teaching of Example 5, [of Capon-130], would have arrived at an embodiment outside the scope of the pending claims, *i.e.* missing a portion of the hinge domain."[53] The Examiner eventually agreed.[54]

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50 Ex. 1021 at 5, 7.

51 Ex. 2034 (3/7/2011 Non-Final Rejection) at 8.

52 *Id.* at 9.

53 Ex. 2109 (3/29/2011 Response) at 19.

54 Ex. 2035 (8/31/2011 Notice of Allowance).

Similar obviousness rejections based on Smith and Capon-130 were imposed during examination of U.S. Appl. No. 08/444,791 ("the '791 application"),[55] which Patent Owner disputed using essentially the same rationale and unexpected results evidence.[56] The Examiner ultimately withdrew those rejections.[57]

**2. The CFAD-IPR**

In 2015, CFAD sought *inter partes* review of the related '522 patent. Like the present Petition, it focused on supposed deficiencies in the original examination's obviousness rejections.[58] For example, it argued the Examiner should have relied on "Capon's 'typical' approach … used in Examples 4 and 5, and FIG.8" of Capon-130, and on the statement in that patent contemplating "enhanced specific activity and modified plasma half-life."[59] CFAD also claimed

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55 Ex. 1023 (6/24/2011 Final Rejection).

56 Ex. 1017 (11/23/2011 Response).

57 Ex. 1025 (2/15/2012 Notice of Allowance).

58 Ex. 1026 (CFAD-Pet.) at 6 ("The Examiner's Smith/Capon rejection was framed incorrectly.").

59 *Id.* at 8–10.

that Capon-130 "disclosed a general method for making [ligand-binding partner]-Fc fusions."[60]

CFAD's obviousness ground was based on U.S. Patent No. 6,004,781 to Seed ("Seed" – Ex. 1027) in view of Smith and further in view of Capon-964. CFAD claimed Seed and Capon-964 "consistently" demonstrated that "chimeric molecules were 'efficiently synthesized' and secreted 'in the absence of any light chain production'"[61] and that an Ordinary Artisan would have been "motivated to create chimeras containing [Smith's] TNF receptor fused to [Seed or Capon-964's] Fc regions because each was expected to express the protein from host cells, to dimerize, resulting in a product with enhanced binding affinity…and because the Fc region provides long serum half-life."[62] CFAD did not directly challenge the unexpected results evidence the Board previously considered, arguing those properties were not "commensurate in scope" with the claims – that they lacked a nexus.[63]

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60 *Id.* at 7.

61 *Id.* at 31.

62 *Id.* at 32–33.

63 *Id.* at 10–11.

The Board declined to institute review.[64] It observed the CFAD petition failed to "offer persuasive evidence to explain why one of skill in the art would choose the Fc portion of the immunoglobulin heavy chain from the choices taught in [Seed or Capon-964]."[65] The Board found (contrary to this Petitioner's assertion) the teaching in Smith regarding "use of the entire constant region would not point to selective deletion of the $C_H1$ domain."[66] The Board also found the unexpected results evidence "commensurate in scope with the claims" and "supports the non-obviousness of the challenged claims," and noted the CFAD petitioner "…should have addressed the evidence of unexpected results as part of Petitioner's showing of a reasonable likelihood of success on the merits."[67]

### B. This Petition Presents a Textbook Case for Denying Institution under §§ 325(d)/314(a)

Each of the criteria the Board has identified in its decisions declining to institute trial based on §§325(d) and 314(a) is present here.

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64 Ex. 1010 at 19.

65 *Id.* at 16.

66 *Id.* at 16–17 (emphasis added).

67 *Id* at 18.

First, the specific teachings of the prior art in this Petition were considered by the Board during original examination and in the CFAD-IPR:

- Smith was considered in both the CFAD-IPR and during examination.[68]
- Watson describes the same pln-HR fusion protein as Example 4 of Capon-964 (upon which the CFAD petitioner based its denied challenge) and of Capon-130 (Ex. 1022) (which was at issue in the appeal to the Board in original examination).[69]
- Zettlmeissl discloses the same CD4-based fusion protein constructs described in the Seed patent (Ex. 1027), which the Board considered in the CFAD-IPR.[70]

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[68] *See supra* § IV.A.

[69] *Compare* Watson at Fig. 1 *with* Ex. 1019 at 40:43–48 *and* Ex. 1022 at 40:24–31; *compare also* Watson at Fig. 1A *with* Ex. 1019 at Fig. 8 *and* Ex. 1022 at Fig. 8. Croft-Decl. ¶¶104–111. Watson was cited as Exhibit 1045 in the CFAD-IPR.

[70] *Compare* Zettlmeissl at 348 ("a 5-amino-acid linker sequence (HADPE), and a synthetic splice donor sequence" was used) *with* Ex. 1027 at 13:20–38 and

The Board has found grounds presenting the same prior art teachings to warrant denial of *inter partes* review.[71] Using redundant secondary references (Zettlmeissl in Ground Two) or reversing the order of the references (Ground One) does not cure this deficiency.[72]

Second, Petitioner employs the same obviousness rationales and justifications advanced in earlier proceedings and found unpersuasive by the Board – it asks the Board to consider Smith, Watson, and Zettlmeissl in substantially the

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Table 2 (showing nucleotides 1292–1306 encoding the HADPE sequence); Croft-Decl. ¶¶162–163. Zettlmeissl also was considered during examination.

[71] *See Nu Mark LLC v. Fontem Holdings 1, B.V.*, IPR2016-01309, Paper 11, at 7–12 (PTAB Dec. 15, 2016).

[72] *See Neil Ziegmann, N.P.Z., Inc. v. Stephens*, IPR2015-01860, Paper 13, at 21 (Sept. 6, 2017) ("Moreover, Section 325(d) does not mention anything about 'relative strengths' of secondary references; it only requires the prior art to be 'substantially the same,' and nothing more.").

same way and for the same purpose as before.[73] The table below maps the positions in this petition to those in the two prior proceedings:

| *Purpose* | *Coherus Arguments* | *CFAD Arguments* | *Prosecution History* |
|---|---|---|---|
| General fusion method makes obvious claimed fusions | Pet. at 33–34. | CFAD-Pet. at 7.<br>CFAD-Pet. at 42. | 3/24/2009 Ex. Answer (Ex. 2045) at 20. |
| Therapeutic uses provide motivation | Pet. at 34. | CFAD-Pet. at 19. | 3/7/2011 Non-Final Rejection (Ex. 2034) at 9. |
| Improved yields and secretion suggest use of hinge-$C_H2$-$C_H3$ | Pet. at 24.<br>Pet. at 36.<br>Pet. at 44. | CFAD-Pet. at 18.<br>CFAD-Pet. at 44. | 3/7/2011 Non-Final Rejection (Ex. 2034) at 8–9. |
| Enhanced binding would motivate | Pet. at 34–35. | CFAD-Pet. at 32–33. | 2/23/2007 Final Rejection (Ex. 2031) at 17. |
| Increase serum half-Life would motivate | Pet. at 35–36. | CFAD-Pet. at 44. | 3/7/2011 Non-Final Rejection (Ex. 2034) at 9. |
| Purification reasons would motivate | Pet. at 37. | CFAD-Pet. at 11. | 3/24/2009 Ex. Answer (Ex. 2045) at 60. |

Third, the Petition presents its arguments as a reply to the Board's past determinations – it thus aims to "second-guess the Office's previous decision on

[73] *See Kingston Tech. v. Polaris Innovations LTD*, IPR2017-00974, Paper 8 at 13 (PTAB Aug. 14, 2017) (declining to institute where each reference "serve[s] the same purpose" as the previously considered art).

substantially the same issue."[74] Indeed, Petitioner frames nearly all of its arguments as solving supposed deficiencies of prior decisions of the Board.[75] Using a new petition to correct supposed deficiencies in an earlier, failed petition is plainly improper.[76]

Accordingly, the Board should exercise its discretion under §§ 325(d) or 314(a) and decline to institute trial.[77] Doing so will avoid wasting the Board's

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[74] *Ziegmann*, IPR2015-01860, Paper 11 at 12–14 (PTAB Feb. 24, 2016).

[75] Pet. at 16–18 (claiming CFAD petition failed to explain why an Ordinary Artisan would "choose the Fc [*i.e.*, hinge-$C_H2$-$C_H3$] portion of the immunoglobulin heavy chain from the choices taught in Seed or Capon."); *see also id.* at 37 ("During prosecution, Patent Owner argued…"); 38 ("Patent Owner argued during prosecution…."), 39 ("Contrary to Patent Owner's arguments…."); 42 ("Patent Owner has previously argued…."). *See also* Ex. 2036 (Coherus Investor Slides) at 21 (publicly portraying Petition as "fundamentally different" from the CFAD-IPR).

[76] *See Gen. Plastic*, Paper 19, at 17–18, n.14 (using the Board's prior decisions as a "roadmap" for future challenges is "unfair to patent owners and is an inefficient use of the *inter partes* review process").

[77] *Huawei Tech. Co., Ltd. v. Pabst Licensing GmbH & Co. KG*, IPR2017-00449, Paper 7, at 9 (PTAB June 12, 2017).

valuable time and resources in revisiting obviousness theories and evidence that have already been fully considered and rejected.[78]

## V. THE PETITION FAILS TO PRESENT ANY BASIS FOR INSTITUTING TRIAL

### A. Ground One: The Claims Are Not Obvious Over Watson in View of Smith

Petitioner asserts the "straightforward application of Watson's method to the 75-kDa TNFR disclosed by Smith...results in a fusion protein that falls within the scope of every claim of the '182 patent."[79] According to Petitioner, an Ordinary Artisan would have been motivated to start with Watson because it supposedly: (i) "teaches use of the IgG fusion protein as an anti-inflammatory" by "block[ing] certain inflammatory pathways" in a manner that "is very similar to the use that Smith and others identified for therapeutics based on TNFR" and (ii) it "teaches a general method to make fusion proteins using various receptors."[80] Petitioner then claims an Ordinary Artisan would have been further motivated to make the

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78 *Hengdian Group DMEGC Magnetics Co., Ltd. v. Hitachi Metals, Ltd.*, IPR2017-01313, Paper 7, at 16 (PTAB Nov. 6, 2017); *Panacea Biotec, Ltd. v. Daiichi Sankyo Co. Ltd.*, IPR2015-01496, Paper 11, at 6 (PTAB Jan. 7, 2016).

79 Pet. at 31.

80 Pet. at 33–34.

claimed TNFR-based fusion proteins because "receptor:IgG fusion proteins were likely to display increased affinity"; that "serum half-life could be greatly extended"; and that "incorporating IgG functionality into a fusion protein" would "simplify purification."[81]

But each of Petitioner's foundational assumptions about Watson is false.

First, following Petitioner's proposed strategy of simply replacing the pln-HR component of Watson's "probe" with TNFR does not yield a fusion protein containing the complete, exon-encoded -hinge-$C_H2$-$C_H3$ portion of IgG, as each of the claims requires – it would yield a fusion protein lacking part of the hinge, and thus fall outside the claims.

Second, Watson does not describe treating inflammation by inhibiting cell signaling pathways, much less in a manner "very similar" to how TNFR-based therapeutics do. Instead, Watson describes a research tool (*i.e.*, a "probe") capable of binding to an unknown ligand and use of this "histochemical reagent" to study physical migration of lymphocytes through peripheral lymph nodes. Watson also did not announce a new, general strategy for making fusion proteins using the claimed hinge-$C_H2$-$C_H3$ portion of IgG heavy chains, but instead indicates the

81 *Id.* at 34–36.

design of its pln-HR-fusion protein was influenced by many different considerations linked to use of its pln-HR fusion as a research tool.

Finally, Petitioner's assertions about supposedly predictable properties shared by the fusion proteins in Watson and the claims ignore numerous, material differences between the involved receptors, ligands and IgG elements, and rest on overgeneralized and scientifically implausible theories.

Petitioner's Ground One rationale also violates a central tenant of the law of obviousness – that an Ordinary Artisan would not make a change that renders a prior art molecule inoperable for its disclosed and intended use.[82] Petitioner's Ground One theory does precisely that – it claims an Ordinary Artisan would start with the Watson pln-HR-IgG protein but then discard the "pln homing receptor" portion of it, the one feature that is both central and necessary to the design, properties and all of the actual and theoretical uses identified in Watson for its "probe."

Petitioner's Ground One theory thus lacks a rational basis based on an objective or accurate depiction of the teachings of the prior art.

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[82] *In re Gordon*, 733 F.2d 900, 902 (Fed. Cir. 1984).

### 1. Petitioner's Combination Would Not Yield the Recited Fusions

Petitioner's Ground One obviousness theory would not have led the Ordinary Artisan to the fusion proteins of the claims for the simple reason that it would yield a fusion protein having a different portion of the IgG heavy chain than what the claims require, and Petitioner provides no reason why an Ordinary Artisan would further modify this fusion protein to contain the correct portion.

Contrary to Petitioner's assertion, Watson's fusion protein does not use the complete hinge-$C_H2$-$C_H3$ portion of the IgG1 heavy chain that the claims require – its protein lacks the first five amino acid sequences of the hinge (including the first cysteine residue) and therefore does not contain "all the domains of the constant region of a heavy immunoglobulin IgG [IgG1] heavy chain other than the first domain of said constant region."[83]

This difference is readily apparent from Watson and related publications describing the structure of Watson's protein. For example, in Figure 1A, Watson states its fusion has only two cysteine residues in its hinge:[84]

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83 Croft-Decl. ¶¶112–118.

84 Watson at Fig. 1A (adapted).

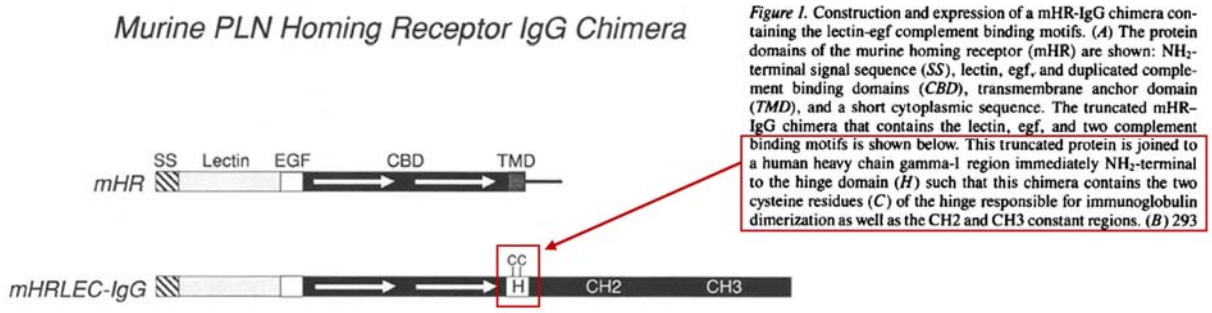


*Figure 1.* Construction and expression of a mHR-IgG chimera containing the lectin-egf complement binding motifs. (*A*) The protein domains of the murine homing receptor (mHR) are shown: $NH_2$-terminal signal sequence (*SS*), lectin, egf, and duplicated complement binding domains (*CBD*), transmembrane anchor domain (*TMD*), and a short cytoplasmic sequence. The truncated mHR-IgG chimera that contains the lectin, egf, and two complement binding motifs is shown below. This truncated protein is joined to a human heavy chain gamma-1 region immediately $NH_2$-terminal to the hinge domain (*H*) such that this chimera contains the two cysteine residues (*C*) of the hinge responsible for immunoglobulin dimerization as well as the CH2 and CH3 constant regions. (*B*) 293

Example 4 of Capon-964, which describes the same pln-HR fusion protein as Watson[85], likewise reports the protein contains only a portion of the hinge: "a sequence beginning in the hinge region just upstream of the papain cleavage site…is described in the Example 4."[86] Patent Owner noted this important difference during the CFAD-IPR, yet, inexplicably, Petitioner ignores it.[87]

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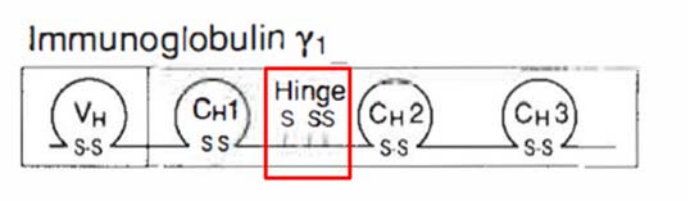
85 Croft-Decl. ¶¶113–115.

86 Ex. 1019 at 15:11–18. *See also* Watson at 2228 ("We thank Dr. Dan Capon for the plasmid construct, containing the human IgG1 constant region, as well as advice on junction sites.") (emphasis added); *cf.* Ex. 1019 at 44:63–66 ("The CD4-Ig plasmid is that described in Capon et al. supra, modified by the deletion of the coding region for the CH1 domain and a portion of the hinge region up to the first cysteine residue.") (emphasis added).

87 Ex. 1010 at 47 (Capon preferred embodiments may contain "…part but not all of the hinge domain…").

As explained in § III.B above, before August 1990, it was well established that the hinge domain of the human IgG1 heavy chain contains three cysteine residues. For example, Ellison shows the human IgG1 hinge domain contains three cysteine residues:[88]


The Capon Nature paper describing Capon's related work similarly shows that the IgG1 hinge contains three cysteines, each capable of forming a disulfide bond.[89]




Petitioner's assertion that the "straightforward application of Watson's method to the 75-kDa TNFR disclosed by [Smith]…results in a fusion protein that falls within the scope of every claim of the '182 patent" is thus demonstrably false.[90]

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88 Ex. 1050 at Fig. 4 (adapted); Croft-Decl. ¶¶66–67.

89 Ex. 1032 at 526 ("The hinge region of each immunoadhesin contains three cysteine residues….").

90 Pet. at 31.

Petitioner compounds its error by providing no reason why an Ordinary Artisan, after supposedly changing pln-HR to TNFR, would then modify Watson's IgG1 portion to add back in the missing hinge residues needed to yield the recited fusion proteins. Petitioner and its expert likewise offer no opinions about whether this change would have any consequences (*e.g.*, whether it would affect expression or secretion of the protein). Both omissions are notable because, throughout its Petition, Petitioner repeatedly emphasizes the supposed criticality of using the same IgG portion as the Watson protein to achieve its supposed benefits.[91]

Petitioner's failure to acknowledge and address this important difference between the IgG portion of Watson's fusion protein and the portion required by the claims is fatal to its Ground One theory.

[91] Pet. at 17 (Watson provides "a clear and compelling reason" to select its fusion location) (emphasis added); *id*. at 18 ("Watson identifies *only one* location as optimal for fusion….") (emphasis in original); *id*. at 40 (modifying Smith based on Zettlmeissl and Watson "results in the exact fusion proteins claimed in the '182 patent") (emphasis added).

### 2. Watson Provides No Motivation for a TNFR Therapeutic

Petitioner's reliance on Watson is also fundamentally misplaced – Watson provides no relevant insights into designing TNF-targeting fusion proteins that can be used to treat inflammatory diseases.

Watson describes investigations of a protein found on murine lymphocytes termed the peripheral lymph node "homing receptor" (pln-HR). Homing receptors are "a set of diverse adhesion receptors on lymphocytes" that bind to carbohydrate structures in tissues and "may be involved in the ability of lymphocytes to home to different anatomical regions…."[92]

To study the physical migration ("trafficking") of lymphocytes through "high endothelial venules" (HEV) within peripheral lymph nodes (pln), Watson prepared a "probe" that combined part of the murine pln-HR protein with part of the human IgG1 heavy chain.[93] Watson stained lymphoid tissue with its probe to identify tissues potentially involved in lymphocyte migration.[94]

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92 Watson at 2221; Croft-Decl. ¶¶73–74.

93 Watson at 2221, Fig. 1.

94 *Id.* ("This murine HR-IgG chimera should prove useful in analyzing the distribution of the HR ligand(s) in normal as well as in inflammatory states."); *see also id.* at 2228 ("it allows for immunohistochemical analysis").

Importantly, as Watson indicates, the cognate ligand of the murine pln homing receptor was "unknown" at the time of its publication.[95] That lack of knowledge plainly limited the conclusions that Watson could draw from its results. For example, while Watson indicates its fusion protein was able to block *in vitro* adherence of lymphocytes to HEV, uncertainty about the cognate ligand precluded Watson from knowing how it achieved that result.[96] Watson also observed that "[a]dditional work will be required to address the physiologic or pathophysiologic significance of the expression of pln HR ligands on pp HEV when it occurs."[97]

Contrary to Petitioner's assertions, Watson nowhere suggests that its fusion protein was able "to block certain inflammatory pathways."[98] Instead, Watson suggested its fusion protein might be able to influence inflammation by interfering with the physical transit of lymphocytes to sites of inflammation, stating:

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95 *Id.* at 2228 ("…the nature of the ligand is currently unknown…").

96 *Id*. (explaining that "[w]hether this [pln endothelial] antigen is the cognate ligand of the mHR-IgG chimera or is sterically close to the ligand is a subject for future investigations.").

97 *Id*.

98 Pet. at 34.

> The demonstrated activity of the chimera in blocking the in vitro adherence of lymphocytes to HEV supports the possibility that leukocyte-endothelial interactions preceding inflammatory responses might be blocked *in vivo*.[99]

Petitioner and its expert fail to appreciate (much less explain) the implications of this observation in Watson. As Patent Owner's expert, Dr. Croft explains, one possible consequence of inhibiting the adherence of lymphocytes to HEV tissue is that those lymphocytes will be diverted to sites in the body where they will exacerbate inflammation – precisely the opposite therapeutic effect.[100]

In fact, Watson itself questions whether its fusion protein could ever be developed into a therapeutic agent. After observing the complexity of the lymphocyte trafficking system, it states:

> [T]he likely involvement of a multiplicity of parallel adhesion systems in leukocyte-endothelial interactions during inflammatory reactions … may limit the efficacy of any particular blocking reagent as an anti-inflammatory drug.[101]

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99 Watson at 2228.

100 Croft-Decl. ¶¶90–92.

101 Watson at 2228.

Before August of 1990, similar uncertainty existed over therapeutically targeting the cytokine TNF. By that time, TNF was known to bind to two different cell surface receptors (*i.e.*, p55 or p75 TNFR) with high affinity.[102] The physiological impact of TNF binding to each receptor, however, was not clearly defined.[103] While some suggested soluble forms of TNFRs had a potential role in mediating the effects of TNF by acting as "scavenge[r]" molecules that blocked messages within the body that lead to or propagated inflammation,[104] others, while acknowledging TNF "may" play a role in inflammatory processes, made clear the "nature of the signal transduced following [TNF-TNFR] association has not been clarified."[105] Moreover, in August of 1990, at least twenty other cytokines had been implicated in inflammation signaling pathways.[106] Indeed, one of the

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102 Ex. 1018 at 231.

103 Ex. 2016 (Heller) ("The physiological significance of soluble [TNF] receptors can at best be only surmised.").

104 Smith at 3:3–6.

105 Ex. 1056 (Beutler) at 514–15 (emphasis added).

106 Ex. 2039 (Lipsky) at 128–129. In August of 1990, IL-1 was believed to have the strongest link to RA. Ex. 2040 (Jacob) at 254 ("The cytokine with the strongest link with rheumatoid arthritis is IL-1.").

references Petitioner's expert cites explains that IL-1, IL-6, IFN-γ, GM-CSF, PDGF, FGF, and TGFß were all cytokines "capable of mediating both stimulatory (agonist) and inhibitory (antagonist) effects" on RA, and the role of TNF "remains to be determined."[107]

In August 1990, an Ordinary Artisan would have recognized the way pln-HR and its unknown ligand might influence an inflammation response (*i.e.*, by regulating migration of lymphocytes to a site of inflammation which could either dampen or enhance inflammation) was materially different than the way TNF and its two receptors (p75 and p55 TNFR) might do so (*i.e.*, influencing intracellular signaling pathways), and that substantial ongoing uncertainty existed about each system.[108]

Petitioner nonetheless claims:

> Watson's proposed use of a receptor:IgG fusion protein to block certain inflammatory pathways is very similar to the use that Smith and others identified for therapeutics based on TNFR.[109]

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107 Ex. 1057 (Arend) at 310–312.

108 Croft-Decl. ¶¶93–97.

109 Pet. at 34 (emphasis added).

But that assertion is supported only by attorney argument – the paragraphs of Dr. Burton's declaration Petitioner cites as support[110] nowhere suggest that an Ordinary Artisan would have considered the way in which a pln-HR fusion protein might "block" inflammation to be "very similar" to the way that a TNF-targeting agent might do so. The lack of evidence supporting this proposition is unsurprising given the very different roles the pln homing receptor and TNF receptors play in the body.[111] The predicate of Petitioner's Watson-based obviousness theory – that pln-HR and TNFR play equivalent roles in inflammation signaling pathways and could be substituted for one another to yield the same result – is false.

### 3. Petitioner's Proposed Change Would Render Watson's Fusion Protein Useless for Its Specified Applications

Petitioner also ignores that its proposed modification to Watson's pln-HR fusion protein (*i.e.*, replacing the pln-HR component with a TNFR component) would remove from Watson's fusion protein its one feature – the pln-HR receptor – that is central to and necessary for every one of the utilities and applications

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110 Pet. at 34 (citing Burton-Decl. ¶¶146–148).

111 *Icon Health & Fitness, Inc. v. Strava, Inc.*, 849 F.3d 1034, 1043–44 (Fed. Cir. 2017) ("[a]ttorney argument is not evidence").

identified in Watson for pln-HR-based fusion proteins. Such modifications are prohibited under the obviousness law.

> Watson identifies several utilities for its fusion protein, explaining:
>
> In the present study, we demonstrate that this chimera exhibits the lectin properties and the adhesion-blocking activity of the native receptor. Additionally, we establish the utility of this protein as a histochemical reagent for staining of pln HEV. The results suggests that the receptor-IgG chimera may prove exceptionally useful in both the isolation of the HEV ligand(s) as well as in the examination of the role of this adhesion system in various inflammatory states.[112]

Every one of these utilities would be vitiated by Petitioner's proposed replacement of the pln-HR element of Watson's fusion protein with a p75 TNFR protein sequence. Without its pln-HR element, Watson's fusion protein could not be used to stain tissues or investigate the role of the unidentified pln-HR ligand(s).[113] Even Watson's speculated therapeutic use of a pln-HR-based fusion protein would be abrogated by the change proposed by Petitioner – the modified TNFR-containing fusion protein proposed by Petitioner would be unable to bind to the unidentified ligand of pln-HR and thus be unable to influence migration of lymphocytes.[114]

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112 Watson at 2222.

113 Croft-Decl. ¶¶98–102.

114 *Id.* ¶101.

Remarkably, Petitioner nowhere acknowledges that its proposed modification would render Watson's fusion protein inoperative for every one of its identified utilities. Instead, Petitioner simply presumes the Ordinary Artisan would make the change, and then tries to justify it post-hoc. Such an analysis is the epitome of hindsight.

Ground One thus fails to meet the central requirement for *prima facie* obviousness – an articulated reason with a rational underpinning as to why an Ordinary Artisan would have selected Watson's pln-HR-based protein and then swapped out its central feature to make a TNFR-based fusion protein.

#### 4. Watson Provides No General Guidance on Fusion Protein Design

Petitioner also contends Watson "discloses procedures of 'general applicability' for preparing fusion proteins comprising a receptor and the hinge-CH2-CH3 portion of the human IgG1 heavy chain."[115] Petitioner's assertions rest on a single sentence in Watson: "the fact that a nonimmunoglobulin superfamily member was successfully produced and employed here suggests that this procedure may be of general applicability."[116]

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115 Pet. at 23, 33.

116 Watson at 2228; Pet. at 23–24.

An Ordinary Artisan would not have read Watson as Petitioner contends (*i.e.*, as being a general guide for producing fusion proteins that calls for use of the particular hinge-$C_H2$-$C_H3$ sequence required by the claims).

Contrary to Petitioner's contention, Watson did not indicate the design of its fusion protein was chosen solely to increase expression. Instead, it identifies numerous factors that influenced that design, including enabling "use of the chimeric protein in histochemical studies employing readily accessible reagents" and that "use of the human IgG1 constant region would eliminate cross-reactivity with endogenous murine IgGs in immunohistochemical staining of mouse lymphoid organs."[117]

Moreover, Watson downplays the criticality of which portion of the IgG heavy chain to use in a fusion protein, explaining:

> The choice of junctional sites between the mHR and human IgG sequences was guided by work with human CD4-IgG chimeras that demonstrated that the joining of the molecules near the hinge region resulted in chimeric molecules that were both efficiently synthesized and dimerized in the absence of any light chain production (9).[118]

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117 Watson at 2224.

118 *Id.* (emphasis added).

Watson also credited Capon (Ex. 1032) for its design choices, which describes fusion proteins with many different designs, including some with a complete (three cysteines) IgG1 hinge plus a $C_H1$ domain and others with a truncated (two cysteines) IgG1 hinge lacking the $C_H1$ domain.[119] Importantly, Capon nowhere correlates increased expression of fusion proteins to the use of different immunoglobulin fragments.[120]

In the CFAD-IPR, the Board considered the Capon group's work as it was described in Capon-964, and found it "does not distinguish the hinge-$C_H2$-$C_H3$ construct as offering any advantage that would lead one of skill in the art to choose it...."[121] According to the Board:

> In fact, [Capon-964] specifically states that the precise site at which the fusion protein is made is not critical, but can be determined by routine experimentation.[122]

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119 Ex. 1032 at Fig. 1; Croft-Decl. ¶¶146–148.

120 Croft-Decl. ¶148.

121 Ex. 1010 at 15; Ex. 1019 at 15:4–11(fusion proteins having full $C_H1$ domain are "particularly preferred embodiments," along with other immunoglobulin constructs).

122 Ex. 1010 at 15 (emphasis added).

The Board also considered the guidance in the Seed patent (Ex. 1027), and found it to likewise not suggest use of the particular IgG portion required by the claims, but to instead suggest multiple potential sites for fusions.[123] The Board thus found the "generalized guidance" that Petitioner flags in Watson insufficient to render the fusion proteins recited in the '522 patent claims obvious.[124]

Petitioner attempts to differentiate its arguments from those in the CFAD-IPR, claiming the references CFAD relied on did not provide "clear guidance as to the best location" for fusion, whereas "Watson identifies *only one* location as optimal."[125] That is incorrect on both points. First, Example 4 of Capon-964 described the same pln-HR fusion protein described in Watson, and was specifically referenced in the CFAD-IPR.[126] Second, Watson (like Capon-964 and Capon) indicated the precise location of fusion <u>is not important</u>, citing Capon, which reported successful expression of fusion proteins with an intact $C_H1$ domain and different portions of the hinge domain.[127] And, of course, Watson described a

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123 *Id.* at 16.

124 *Id.* at 15.

125 Pet. at 17–18 (emphasis in original).

126 Croft-Decl. ¶¶103–111; Ex. 1010 at 10–11.

127 Croft-Decl. ¶¶146–147.

fusion protein that contains a different portion of the IgG1 hinge than what the claims require.[128]

Watson thus did not teach (as Petitioner contends) a method of "general applicability" for preparing fusion proteins having the same IgG portion required by the claims. Instead, it taught the same thing as Capon-964 – that there is no criticality of the precise portion of the IgG heavy chain to use in a fusion protein.

### 5. Petitioner's Hindsight-Based Reasons Would Not Have Motivated an Ordinary Artisan to Make the Proteins

Petitioner lists a number of supposedly desirable properties of a p75 TNFR fusion protein, such as binding affinity, half-life, and ease of purification, and asserts that to achieve them, an Ordinary Artisan "was motivated to apply Watson's method to Smith's TNFR to make a TNFR:hinge IgG fusion protein…."[129] But under Petitioner's Ground One obviousness rationale, an Ordinary Artisan would supposedly start with Watson's pln-HR fusion protein and then modify it to include the TNFR sequence disclosed in Smith. Given that the "solutions" to these various theoretical problems are not provided by Smith, there would have been no reason for the Ordinary Artisan to consider the latter reference for motivation. In reality, each of Petitioner's supposed motivations is simply a

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128 *See supra* § V.A.1.

129 Pet. at 33–36.

post hoc justification based on hindsight, not the beliefs of an Ordinary Artisan in August of 1990. None would have led the Ordinary Artisan to the claimed fusion proteins.

a. Binding Affinity Would Not Have Provided a Motivation

Petitioner asserts an Ordinary Artisan would have been motivated to make the claimed TNFR-fusion proteins because such proteins "were likely to display increased affinity for their target compared to the soluble receptor alone."[130] But Petitioner identifies nothing to suggest that in August 1990 an Ordinary Artisan would have believed increasing the binding affinity of p75 TNFR was necessary or would provide any specific therapeutic benefits.

Initially, Petitioner ignores knowledge in the prior art that soluble and cell-bound forms of p75 TNFR already bind TNF with high affinity. Smith, for

130 Pet. at 34.

example, reports $K_a$ values of 1 x $10^{10}M^{-1}$ and 1 x $10^{8}M^{-1}$.[131] These affinities are comparable to "high affinity" monoclonal antibodies.[132]

Petitioner also provides no reason why an Ordinary Artisan would have believed enhancing the binding affinity of p75 TNFR would have been desirable or necessary to use TNFR fusion as an anti-inflammatory. Watson, for example, does not suggest it is necessary – it reports that its bivalent pln-HR fusion protein bound in a "quantitatively similar" way relative to soluble pln HR.[133]

Finally, while Petitioner cites Smith as observing that "polyvalent forms of TNF-R may have enhanced binding affinity for TNF ligand," Petitioner ignores that Smith already describes a "polyvalent" "chimeric" antibody,[134] as well as other

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131 Smith at 18:41–49; *see also* Ex. 1058 (Engelmann-1990) at 1532–33 (soluble p75 TNFR "specifically binds" TNF").

132 Ex. 2041 (Huston) at 5879 ("The [anti-digoxin] antibody exhibits a high digoxin binding affinity ($K_a$=5.4 x $10^{9}$ $M^{-1}$)…providing a baseline for comparison with the biosynthetic sFv.").

133 Watson at 2224.

134 Smith at 10:53–68

"polyvalent forms of TNF-R" (*e.g.*, chemically conjugating two p55 TNFR molecules using polyethylene glycol).[135]

b. Half-Life Would Not Have Provided a Motivation

Petitioner next asserts an Ordinary Artisan would have been motivated to produce TNFR-based fusion proteins to improve its half-life in the body.[136] But Petitioner again points to nothing that shows in August 1990 an Ordinary Artisan would have believed increasing the half-life of a p75 TNFR protein was necessary or desirable.

The pre-1990 literature actually suggests the contrary. For example, one group hypothesized in 1989 that native forms of soluble TNFR "might prolong the exposure of the organism to endogenously produced TNF by binding the cytokine and then releasing it slowly in an active form."[137] Petitioner and its expert cite other work from this research group (Ex. 1058) but ignore this disclosure.

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135 *Id.* at 10:33–44. In fact, others had tried this latter approach with the p55 TNFR around the time of the invention, but failed. *See* Ex. 2042 ('866 patent) at 38:67–39:2.

136 Pet. at 35–36.

137 Ex. 2021 (Engelmann-1989) at 11979.

Even if an Ordinary Artisan had a reason to increase the half-life of a p75 TNFR-based protein, that person would have had no reason to look to Watson for a solution. For example, Smith explains a protein's half-life can be increased using pegylation or through chemical linkage of two TNFR molecules.[138] It also had been shown before August 1990 that the half-life of cytokines, such as IL-2, could be increased by pegylation.[139]

Petitioner attempts to remedy these analytical gaps by citing the inventors' own subjective insights regarding half-life.[140] That is improper and cannot provide a motivation for establishing obviousness.[141]

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[138] Smith at 10:33–44.

[139] Ex. 2043 (Katre) at 209 (pegylated IL-2 exhibited "enhanced solubility, longer circulatory life, and increased potency").

[140] Pet. at 35–36.

[141] *Zoltek Corp. v. U.S.*, 815 F.3d 1302, 1313 (Fed. Cir. 2016) ("arguments reliant upon ex post reasoning," including expert testimony that relies on the teachings of the patent itself and the other disclosures of the inventor, shows "hindsight bias").

c. Purification Would Not Have Provided a Motivation

Petitioner next asserts an Ordinary Artisan would have been motivated to combine Watson and Smith to obtain "practical yields" of TNFR and to "simplify purification of the receptor."[142] But Examples 7 and 8 of Smith describe examples where soluble TNFR was successfully produced in CHO cells and in yeast, and Smith describes well-known techniques (*e.g.*, affinity chromatography using the target ligand or monoclonal antibodies, reverse phase high performance liquid chromatography,[143] or use of poly-histidine ("poly-His") tags or linkage to other amino acid sequences[144]) to purify the receptor. Many of these methods had been used to purify soluble forms of TNFR before August of 1990.[145]

If Petitioner's Ground One arguments are based on a desire to make a p75 TNFR-based therapeutic, there is simply no reason why an Ordinary Artisan would

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142 Pet. at 36.

143 Smith at 16:4–23.

144 *Id.* at 7:54–66.

145 Ex. 1058 at Abstract (use of "ligand (TNF)-affinity purification, followed by reversed phase high performance liquid chromatography."); Ex. 2044 (Brockhaus) at 3129 ("TNF binding proteins were enriched from cell lysates by TNF-α affinity chromatography").

have started with Watson. All the benefits that Petitioner claims the IgG component of Watson provides are addressed using other means in Smith. Only through the lens of hindsight would the two references be considered together.

### B. Ground Two: The Claims Are Not Obvious Over Smith in View Of Zettlmeissl and Watson

Petitioner's Ground Two posits that an Ordinary Artisan would have found each of the claims obvious based on Smith in view of both the Zettlmeissl and Watson references.[146] Supposedly, the Ordinary Artisan would start with the "chimeric" TNFR substituted antibody structures disclosed in Smith and modify them to instead use only the hinge-$C_H2$-$C_H3$ IgG sequence. The sole reason Petitioner offers for doing this is that, purportedly:

> Zettlmeissl and Watson taught that removing the $C_H1$ region and the light chain of the IgG immunoglobulin would optimize expression of the fusion protein.[147]

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[146] Pet. at 40. The Petition improperly intermingles quotes from these two references, rather than clearly identifying what is missing from the various combinations of each with Smith.

[147] Pet. at 40 (emphasis added).

According to Petitioner, a "POSA would have recognized that Zettlmeissl and Watson report optimized methods for preparing fusion proteins compared to Smith's earlier disclosure."[148]

But this rationale is based entirely on attorney argument – Petitioner cites no evidence suggesting any problem actually existed with expressing the decidedly different TNFR fusion proteins described in Smith. Zettlmeissl also nowhere "compare[s]" expression of fusion proteins like those in Smith (*i.e.*, with light chains), as Petitioner suggests.[149] Further, Petitioner's theory requires the Ordinary Artisan to ignore the explicit guidance in Smith to use "unmodified constant region domains" in TNFR-based fusion proteins. And Petitioner's rationale is also the same one the Board specifically rejected in the CFAD-IPR as being insufficient to suggest modifying Smith's TNFR-based fusion proteins to obtain "practical yields." The Board should reject this rationale again.

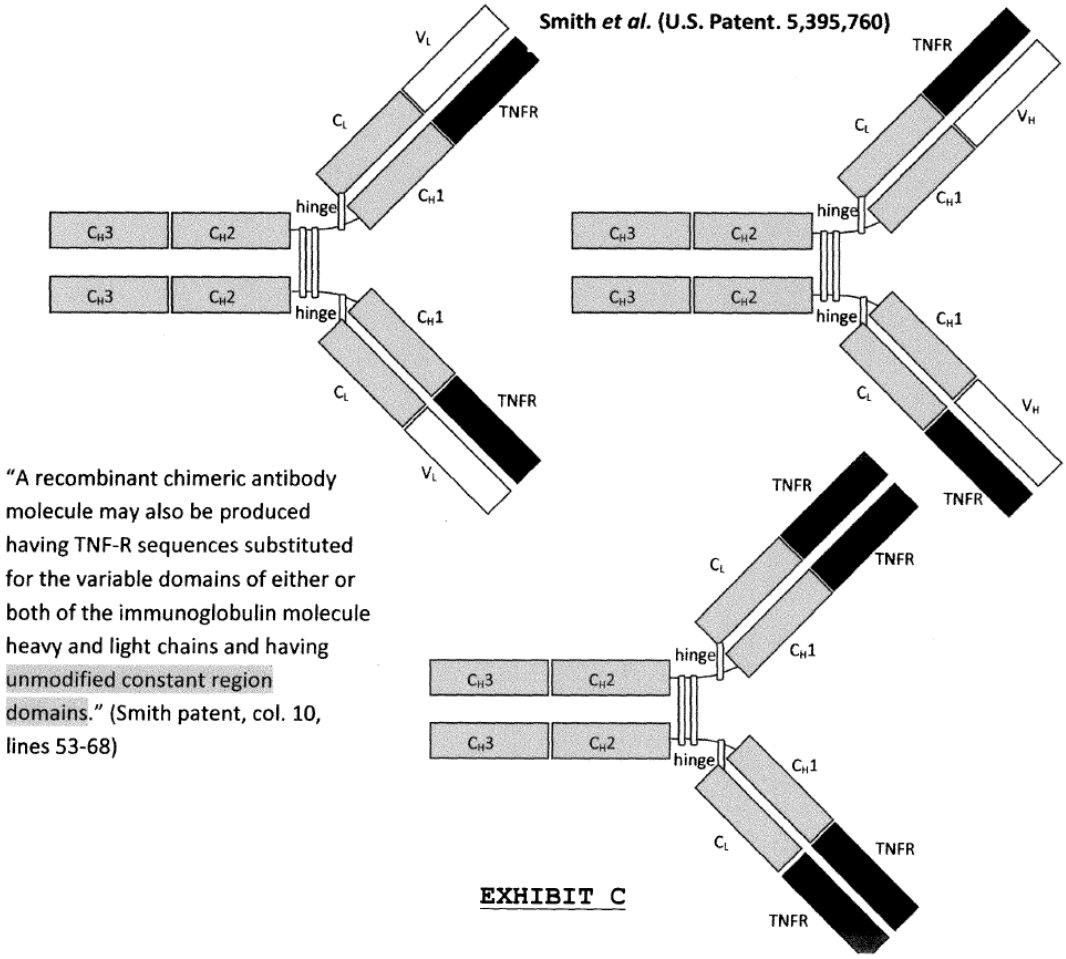
**1. Ordinary Artisans Would Not Disobey Smith's Guidance**

Smith describes very different TNFR-based fusion proteins than the claims – in which the variable domain of one or both of the heavy and light chains is replaced with a TNFR sequence, but which otherwise retain the conventional

148 Pet. at 45.

149 *Id.*

tetrameric structure of an immunoglobulin, including the $C_H1$ and $C_L$ domains (illustrated in figure below):[150]




Smith also makes clear that TNFR-based fusion proteins should retain "unmodified" heavy and light constant regions.[151] Smith cites two different patent publications where "[a]dditional details relating to the construction of such

150 Ex. 2037 (8/11/2011 Response) at Ex. C. *See also* Pet. at 3.

151 Smith at 10:53–61.

chimeric antibody molecules" can be found.[152] Neither suggests modifying the design of the fusion proteins in Smith.[153]

As the Board found in the CFAD-IPR, an Ordinary Artisan would find no reason within Smith to modify the tetrameric fusion proteins it describes, particularly in a way that disobeys its explicit guidance to use "unmodified" constant regions (*i.e.*, that include the light chain constant domain and the heavy chain $C_H1$ domain).[154]

### 2. Zettlmeissl's Teachings Belie Any "Expression" Problem

The linchpin of Petitioner's Ground Two rationale is its theory that an Ordinary Artisan would have been motivated to "optimize" expression of Smith's tetrameric TNFR fusion proteins because Zettlmeissl and Watson supposedly teach this goal can be achieved by "attach[ing] the extracellular receptor at the hinge region of the IgG heavy chain."[155] But Zettlmeissl's comments concerning relative

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152 *Id.* at 10:66–68.

153 Croft-Decl. ¶143.

154 Ex. 1010 at 15–16.

155 Pet. at 42, 45 ("A POSA would have recognized that Zettlmeissl and Watson reported optimized methods for preparing fusion proteins compared to Smith's earlier disclosure.") (citing Burton-Decl. ¶¶160, 166).

expression levels of fusion proteins relate to fusion proteins that, like Watson's protein, were not expressed with a light chain constant domain.[156] That is a critical point – as Zettlmeissl itself makes clear, expression problems are not ordinarily encountered when immunoglobulin structures are expressed with a light chain constant region:

> The presence of either IgG or IgM $C_H1$ domains correlated with markedly reduced fusion expression, a result not entirely unexpected, given that $C_H1$ is normally found associated with either a light-chain constant region or heavy-chain binding protein during the course of synthesis in B cells (Haas and Meo, 1988).[157]

An Ordinary Artisan thus would have understood Zettlmeissl's observations about expression to concern fusion proteins not expressed with a light chain constant

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[156] Zettlmeissl reports preparation of two kinds of "CD4:IgG" fusion proteins. Zettlmeissl at Fig. 1. One retained the $C_H1$ domain, but did not include the associated $C_L$ domain, while the other removed both the $C_H1$ and $C_L$ domains. *Id.* Zettlmeissl reports the presence of the $C_H1$ domain "correlated with markedly reduced fusion expression." *Id.* at 352; Croft-Decl. ¶¶138–142.

[157] Zettlmeissl at 352.

domain.[158] Indeed, Capon shows these types of expression problems were not even consistently observed.[159]

Petitioner and its expert nowhere discuss the implication of this critical observation in Zettlmeissl – that expression problems would not have been expected for Smith's tetrameric fusion proteins.[160] It is all the more remarkable because Petitioner and its expert plainly recognized that Smith's fusion proteins are expressed with light chains.[161] Petitioner's supposed motivation to "optimize" expression of Smith's fusion proteins is thus illusory.[162]

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158 Croft-Decl. ¶142.

159 Ex. 1032 at 526 ("CD4-heavy-chain hybrids…containing either the first two or all four immunoglobulin-like domains of CD4 (named 2γ1 and 4γ1 respectively), were secreted in the absence of wild-type or hybrid light chains (Fig. 2a).") (emphasis added); Croft-Decl. ¶148.

160 Petitioner makes no mention of Zettlmeissl's observation in the petition. Dr. Burton quotes it twice but nowhere addresses its significance. *See* Burton-Decl. ¶¶86, 165.

161 *See, e.g.*, Pet. at 3, 41 (showing Smith fusion protein containing light chains); Burton-Decl. ¶57 (identifying the "Light Chain").

162 Croft-Decl. ¶¶141–142.

Petitioner next claims that an Ordinary Artisan would have been somehow motivated to alter Smith's fusion proteins by "joining the extracellular TNFR to the IgG1 heavy chain at the hinge region, omitting the light chain and the CH1 region of the heavy chain."[163] But Petitioner and its expert identify nothing in Zettlmeissl or Watson that supports that proposition. Instead, they simply presume doing that would be desirable for all fusion proteins, regardless of the nature of the fusion.[164] Petitioner's non-existent expression level problem thus cannot support a finding of obviousness.[165]

Petitioner also argues that "[t]he POSA also was motivated to prepare TNFR:IgG fusion proteins for all the reasons discussed in Section IX.A.2 above" (Ground One).[166] The same reasons why Ground One is deficient apply to Ground Two. Also, Petitioner nowhere explains why an Ordinary Artisan would have

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163 *E.g.*, Pet. at 5, 42, 45.

164 *Id.* at 43–45 (emphasis added).

165 *Leo Pharm. Products Ltd. v. U.S.P.T.O.*, 726 F.3d 1346, 1354 (Fed. Cir. 2013) ("[B]ecause neither Dikstein nor Serup recognized or disclosed the stability problem, the record shows no reason for one of ordinary skill in the art to attempt to improve upon either Dikstein or Serup using Turi.").

166 Pet. at 48.

believed Smith's "chimeric" antibody would need binding, half-life, or purification improvements.[167]

### 3. Petitioner's Ground Two Combination Would Not Yield the Recited Fusions

As it did in Ground One, Petitioner glosses over material differences in the structures of Zettlmeissl's and Watson's fusion proteins relative to what the claims require, and incorrectly contends that "modifying Smith's TNFR:IgG fusion proteins as taught by Zettlmeissl and Watson results in the exact fusion proteins recited in the '182 Patent claims."[168]

As explained in § V.A.1, Watson's fusion protein does not use the same IgG1 sequence required by the claims. Zettlmeissl similarly has material differences in the design of its fusion proteins relative to the claims – each interposes an artificial five amino acid linker sequence between the receptor and

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[167] Croft-Decl. ¶¶138, 140, 142–143.

[168] Pet. at 40. *See also* Pet. at 5 (arguing Watson and Zettlmeissl use "the identical portion of the IgG heavy chain as" in the contested claims).

immunoglobulin sequences.[169] Following Petitioner's rationale of replacing only the "receptor" in its proposed combination of Smith with both Zettlmeissl and Watson would thus yield fusion proteins that include a third component (*i.e.*, an artificial "linker") between the receptor and IgG components and omit part of the hinge. Remarkably, Petitioner never explains why an Ordinary Artisan would change Watson's IgG component to add residues that yield the complete hinge required by the claims.[170] As to Zettlmeissl's linker sequence, Petitioner takes inconsistent positions. First, Petitioner refuses to even acknowledge its presence.[171] Then, later in the Petition, Petitioner admits it is present in the Zettlmeissl fusion constructs, but in a conclusory assertion claims an Ordinary Artisan would remove it because it was "unnecessary."[172] That assertion conflicts not only with Petitioner's other assertions (*e.g.*, that Watson taught "only one

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169 Zettlmeissl at 348 ("The fusions were accomplished with the aid of a joining oligonucleotide encoding a 5-amino-acid linker sequence (HADPE)…."); Croft-Decl. ¶¶154–156.

170 Pet. at 22–24, 28–33.

171 *Id.* at 4; *id.* at 44 ("the receptor was fused to the hinge region of an IgG1 heavy chain").

172 *Id.* at 50.

location as optimal for fusion" and that Watson and Zettlmeissl both "directed the POSA to choose exactly" the immunoglobulin component of a TNFR-based fusion protein"[173]), but Dr. Arora's Declaration during original examination showing that changes at the junction of the TNFR and IgG portions can have functional consequences.[174]

Petitioner thus has entirely failed to articulate a rational basis why an Ordinary Artisan would have modified the teachings of Smith based on the disclosures of Zettlmeissl and Watson in a way that would yield the claimed invention. The Board should decline to institute trial on Ground Two.

## VI. OBJECTIVE INDICIA OF NON-OBVIOUSNESS CONFIRM THE PATENTABILITY OF THE INVENTION

The Federal Circuit has emphasized that real-world evidence concerning how a patent has been received is a critical safeguard against hindsight.[175] Such

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173 *Id.* at 18 (emphasis added to second term).

174 Ex. 1024 ("Arora-Decl.") ¶¶2–4 (explaining the structure of the tested constructs; *id.* at ¶¶5–6, Exhibits C–D (explaining and showing results of CDC/ADCC assays).

175 *Crocs, Inc. v. ITC*, 598 F.3d 1294, 1310 (Fed. Cir. 2010).

objective indicia are important in any obviousness analysis and "it is an error not to consider them."[176]

Surprisingly, while the petition takes issue with certain unexpected results of etanercept previously considered by the Board, it is entirely silent on other objective indicia associated with etanercept, including that it: (i) met a long-felt need and was praised, (ii) enjoys substantial commercial success, (iii) was copied by others, and (iv) succeeded where other fusion proteins failed. Petitioner's silence is inexcusable, given that it recognizes the claims cover etanercept,[177] that etanercept is one of the world's most successful RA drugs, and that Petitioner is most certainly aware of etanercept's remarkable attributes given its multi-year campaign to copy it.

Consequently, even if Petitioner had somehow made out its *prima facie* case (it did not), the Board should deny institution due to the numerous uncontested objective indicia of non-obviousness associated with etanercept.

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176 *In re Kao*, 639 F.3d 1057, 1067 (Fed. Cir. 2011).

177 Ex. 2003 (Coherus 10-K) at 50 ("…Brockhaus, et al., U.S. patents 8,063,182 and 8,163,522…are directed to the fusion protein in Enbrel.").

### A. Etanercept Has a Nexus to the Contested Claims

Despite being a central issue during prosecution of the '182 patent and the CFAD-IPR, Petitioner does not dispute that a nexus exists between the objective indicia of etanercept and the claims of both the '182 and '522 patents – it nowhere suggests the Board's prior findings of such a nexus were wrong.[178] A nexus is presumed here because etanercept falls within the scope of the claims,[179] as Petitioner itself admits.[180] The Board should not revisit this issue, but should instead maintain its prior findings regarding nexus.

### B. Numerous Uncontested Objective Indicia of Etanercept Demonstrate the Claims Are Not Obvious

Petitioner, despite its intimate familiarity with the commercial and clinical profile of etanercept, presents no arguments and no evidence concerning numerous types of objective indicia of non-obviousness linked to etanercept. Given that each

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178 *See* Ex. 1021 at 7 (crediting unexpected results of etanercept as objective indicia of non-obviousness); Ex. 1010 at 18 (finding objective indicia evidence based on etanercept to be "commensurate in scope with the claims.").

179 *E.g.*, *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1329 (Fed. Cir. 2016); Croft-Decl. ¶¶32–35, 53.

180 Ex. 2003 at 50; *see also* Croft-Decl. ¶¶32–35, 53.

has a nexus to the claims, the Board should credit them – individually and collectively – as supporting the non-obviousness of the claims.

### 1. Etanercept Is Praised and Met a Long-Felt Unmet Medical Need

Before etanercept, drugs used to treat RA patients failed to control clinical signs and symptoms of the disease, halt advancement of the disease, or maintain patient function in a majority of patients.[181] These pre-etanercept treatments included NSAIDs, steroids, and conventional synthetic disease modifying anti-rheumatic drugs ("csDMARDs"), such as sulfasalazine.[182] Even the cornerstone RA therapy, methotrexate ("MTX"), provided benefits in only about 30% of patients using one standard RA metric; MTX also was associated with severe side effects.[183] Thus, before etanercept, there was a demonstrated need for a safe and effective treatment that would halt disease progression (*e.g.*, joint destruction) in rheumatoid arthritis patients.[184] Indeed, such a drug was considered by some to be

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181 Ex. 2046 (Fleischmann-Decl.) ¶¶23–30.

182 *Id.* ¶¶24–26.

183 *Id.* ¶¶27–28.

184 *Id.* ¶¶29–30.

the "holy grail."[185]

As Petitioner is well-aware, etanercept met that long-felt unmet medical need – it is able to halt the progression of the debilitating symptoms of RA in the vast majority of treated patients, and has dramatically improved the lives of many patients.[186] Etanercept also has been hailed as a "breakthrough" therapy[187] that set the precedent for other TNF-inhibitor drugs, such as Humira® (adalimumab) and Remicade® (infliximab), which the FDA has recognized have "revolutionized" the treatment of inflammatory diseases.[188]

Indeed, respected rheumatologists have observed that etanercept is such a "dramatic drug that many patients now appreciate a new way of life," and that TNF-inhibitors like etanercept were "an exciting development" that gave doctors a powerful new tool in the control of a potentially fatal disease.[189]

Notably, neither Dr. Burton nor Petitioner even acknowledge the unmet medical need etanercept addressed or its praise from others.

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185 *Id.* ¶30.

186 *Id.* ¶36.

187 *Id.* ¶34.

188 Ex. 2030 (FDA AAC Transcript) at 134.

189 Fleischmann-Decl. ¶41.

### 2. Etanercept Is Commercially Successful

"When 'a product attains a high degree of commercial success, there is a basis for inferring that attempts to a solution have been made and have failed.'"[190] Petitioner turns a blind eye to the clinical, commercial success of etanercept.

Within two years of its approval, most rheumatologists began using etanercept as the treatment of choice in the approximately 70% of patients who still had active disease despite treatment with methotrexate.[191] The demand for etanercept exceeded all expectations.[192] By December 2001, approximately 121,000 patients had been treated with etanercept – a rare accomplishment for an injectable drug based on an entirely new mechanism of action – and about 20,000 patients were on the waiting list for etanercept by 2002.[193]

Etanercept had (and continues to have) a substantial share of the RA therapy market. For example, after its launch in 1998, etanercept use grew rapidly to over half a million monthly prescriptions per year by 2000, remained around that level through 2002, then sharply grew to just under two million monthly prescriptions by

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190 *WBIP*, 829 F.3d at 1330–31.

191 Fleischmann-Decl. ¶37.

192 *Id.* ¶38.

193 *Id.*

2006 and remained around that level through 2008.[194] This growth occurred despite the market entry of two other biological-DMARDs ("b-DMARDs"), Remicade® and Humira® in 1999 and 2003, respectively.[195]

Etanercept's high utilization was reflected among all categories of RA patients. Among privately insured patients, etanercept was the most prescribed first-line b-DMARD from 2005-2008.[196] Among Medicaid patients, etanercept was the most prescribed first-line b-DMARD from 2001-2008.[197] Thus, there was a "sustained preference for etanercept as the agent of choice for patients initiating new treatment episodes with bDMARDs."[198] Etanercept was also the most used self-injectable biologic for treating RA among the Medicare population in 2007-2008, following its inclusion in the Medicare plan after the implementation of Medicare Part D in 2006.[199]

Etanercept's commercial success is plainly attributable to its properties,

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194 Carter-Decl. (Ex. 2083) ¶25.

195 *Id.* ¶27.

196 *Id.* ¶29.

197 *Id.* ¶¶29–30.

198 *Id.* ¶29.

199 *Id.* ¶30.

which in turn are based on its unique structure.[200] Enbrel®'s rapid and sustained utilization confirms that etanercept's efficacy and safety profile, as confirmed by its long history of physician and patient demand and use, is primarily responsible for its commercial success, as compared to other extraneous factors.[201]

Petitioner is plainly aware of etanercept's commercial success. It based its decision to copy this product on that knowledge. In its Annual Report, Petitioner also identifies etanercept as a "blockbuster drug" and indicates it selected etanercept for biosimilar development because its presents a "[l]arge market opportunity."[202] Petitioner inexplicably fails to even mention the clinical and commercial success of etanercept.

### 3. Etanercept Has Been Copied by Others

Within the United States, at least two companies – including Petitioner Coherus – have expended substantial efforts and resources to copy etanercept. For

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200 Ex. 2079 (Moreland-1998) at 582 ("The resulting immunoglobulin-like dimer….has a substantially higher affinity for TNF-α than monomeric soluble receptor….[and] the immunoglobulin-like Fc structure results in a longer half-life of the molecule in vivo.").

201 Carter-Decl. ¶¶35–37, 39–40, Figs. 2–4.

202 Ex. 2003 at 4, 12.

example, Sandoz Inc. represented to the FDA that it sought to make its product as identical as possible to etanercept in Enbrel®, copying not only its exact amino acid sequence but its CHO-cell production method.[203]

Petitioner makes no observations on this copying evidence, despite being one of the entities most knowledgeable about it.

**4. Failure of Others**

Petitioner devotes extensive efforts portraying the fusion proteins described in Smith, Watson and Zettlmeissl as rendering obvious the recited fusion proteins of the claims. But Petitioner nowhere reveals that none of those prior art fusion proteins was successfully advanced as a clinical or commercial product.

For example, CD4 receptor proteins started clinical trials for HIV, but were discontinued in Phase I in 2005.[204] Likewise, there is no evidence Watson's fusion proteins were ever successfully developed, especially a therapeutic for treating inflammation, an unsurprising outcome given Watson's own skepticism.[205]

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[203] Ex. 2008 (Advisory-Committee Slides) at CA-5, CA-14; Ex. 2027 (Summary-Review) at 4.

[204] Ex. 2107 (CD4-IgG Drug Profile) at 1.

[205] Watson at 2228.

Petitioner also ignores the failed efforts of others to develop TNFR-based products. For example, one group tried but failed to develop a dimeric pegylated p55 TNFR product but, as one report explained, "[t]his TNFbp will not be a viable option for treating patients with RA secondary to immunogenicity."[206]

"While absolute certainty is not necessary to establish a reasonable expectation of success, there can be little better evidence negating an expectation of success than actual reports of failure."[207]

### C. Petitioner's Flawed Scientific Analysis is Inadequate to Explain Away Evidence of Etanercept's Unexpected Results

Ignoring other known objective indicia of non-obviousness having a nexus to etanercept, Petitioner takes issue with only certain of the unexpected results the Board considered during original examination and in the CFAD-IPR. But even for those, Petitioner's criticisms lack any merit.

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206 Ex. 2032 (Moreland-2000) at 601, 607 ("further development of the TNFbp dimer for chronic RA [rheumatoid arthritis] became a concern because of the immunogenicity of this dimerically linked PEGylated molecule").

207 *Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp.*, 320 F.3d 1339, 1354 (Fed. Cir. 2003).

### 1. Etanercept's Binding Properties Were Unexpected

Petitioner first contends the enhanced binding and neutralization properties of etanercept and its lack of aggregation were all somehow expected because it was known before August of 1990 that "multiple" soluble TNFR monomers can bind the TNF trimer.[208] All of Petitioner's arguments concerning unexpected results rest on this assertion, and because it is false, each of those arguments should be dismissed.[209]

Petitioner's expert, Dr. Burton, cites two papers for the proposition that it was established by August 1990 that multiple soluble TNFRs bind a single TNF trimer.[210] Neither paper supports his assertions. The first simply confirms that TNF exists in solution as a trimer while the second reports that multiple proteins,

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[208] Pet. at 54–58, 63.

[209] Pet. at 56 (binding: "POSAs also knew that multiple TNF receptors bind a single TNF molecule."); *id*. at 57 (neutralization: "TNFR-fusion proteins" "were expected to bind multivalently with the trimeric TNF molecule."); *id*. at 64 (aggregation: "POSAs had good reason to expect that both receptors on the dimeric TNFR:IgG fusion protein would bind a single TNF ligand, because it was known that multiple TNF receptors on the cell surface bind to a single TNF molecule.").

[210] Burton-Decl. ¶184 (citing Ex. 1036 at 6951; Ex. 1037 at 14646).

including at least one TNFR, on the cell surface interact with the TNF trimer. Neither paper provides insights into how many soluble TNFRs can separately bind a TNF trimer.[211] And subsequent papers, citing this same work, confirm Dr. Burton's reading is wrong – one explained that cell-bound TNFRs self-associate (*i.e.*, "crosslink") rather than separately bind different TNF ligands within a TNF trimer, [212] while another observes that "one TNFα trimer binds to one receptor molecule" citing the second paper Dr. Burton relies upon.[213]

In short, the premise underpinning each of Petitioner's challenges to etanercept's unexpected binding, neutralization, and aggregation properties is false – in August 1990, it was not known how many soluble TNFR proteins could simultaneously bind to a single TNF trimer. An Ordinary Artisan– even under Petitioner's reasoning – could not have predicted that the TNFR fusion protein of the claims binds TNF with a 50-fold greater affinity than a TNFR monomer, exhibits a 1000-fold increase in neutralization of TNFα and does not cause aggregation.[214]

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211 Croft-Decl. ¶¶196–202.

212 Ex. 2010 (Schall) at 367–68; Croft-Decl. ¶200.

213 Ex. 2022 (Hohmann) at 14929 (emphasis added); Croft-Decl. ¶201.

214 Croft-Decl. ¶¶190–191, 210–216.

Moreover, knowledge of the stoichiometry of soluble TNFR binding to TNF trimers would not have enabled an Ordinary Artisan to predict how a bivalent TNFR fusion protein – which presents two TNFRs in an unnatural configuration – might interact with TNF trimers.[215] And without any information illuminating how a bivalent TNFR-based fusion protein interacts with TNF trimers, an Ordinary Artisan could only have made the most general of assumptions.

For example, an Ordinary Artisan might have envisioned a bivalent TNFR fusion protein interacting with a TNF trimer in the ways an antibody can interact with a multimeric antigen – by binding two TNF ligands in separate trimers, by binding two TNF ligands in the same trimer, and/or by binding only one TNF ligand if its other arm cannot bind another TNF ligand (whether in the same or a different trimer).[216]

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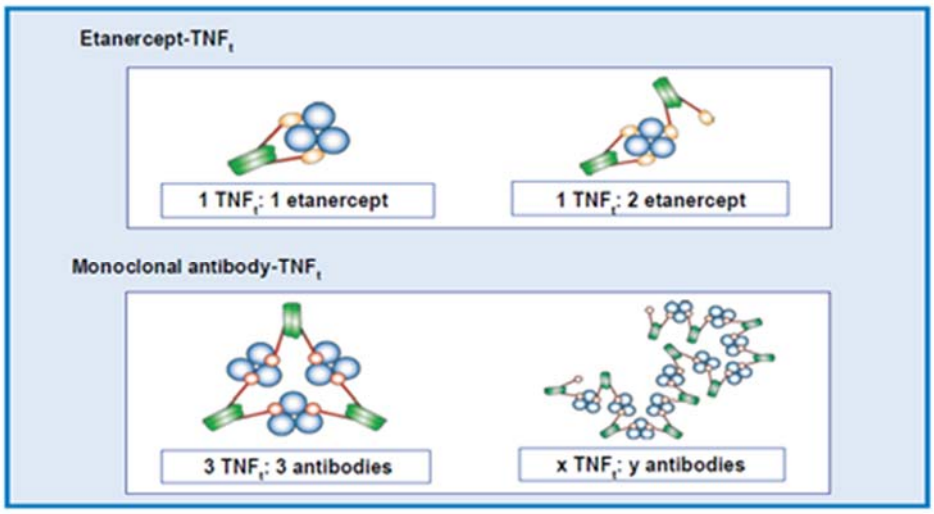
[215] Croft-Decl. ¶202 (explaining stoichiometry would not explain whether TNFR presented in constrained IgG-based molecule could bind multiple TNF ligands or cause aggregation).

[216] *See* Croft-Decl. ¶¶204–209 (citing Ex. 2023 (Thomas) as explaining antibodies have ability to exhibit "monogamous" and "bigamous" binding interactions with a multimeric antigen).

An Ordinary Artisan likewise would have expected etanercept to cause aggregation like anti-TNF antibodies because it is bivalent, like an antibody. Aggregation results when many bivalent TNF-binding molecules (*e.g.*, antibodies or TNFR multimers) bind different TNF trimers with their different arms, leading to the formation of higher order oligomeric complexes of antibodies and TNF trimers (shown in bottom panel below).[217]




Etanercept surprisingly does not cause aggregation while anti-TNF antibodies do – testing showed it binds only a single TNF trimer, and does not

[217] Ex. 2024 (Kohno-2005); Croft-Decl. ¶208.

cause higher order oligomeric complexes to form, unlike anti-TNF antibodies.[218] Neither the flexibility of an Ig structure lacking the $C_H1$ domain nor anything else known in August of 1990 would have enabled an Ordinary Artisan to predict this effect. Indeed, Petitioner seeks to have it both ways: it cites etanercept's similarity to conventional antibodies to claim its binding and neutralization properties were expected, but its differences from conventional antibodies to claim its lack of aggregation was expected.[219] Both assertions are simply hindsight.

**2. Etanercept's ADCC and CDC Profile Was Unexpected**

Petitioner also disputes it was surprising that etanercept exhibited low ADCC and CDC activities despite its incorporation of portion of an IgG1 heavy chain.[220] Here, it asserts that nothing in the prior art "taught away from using an

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[218] Croft-Decl. ¶¶207–208, 210–216 (explaining aggregation results when a bivalent TNF binding molecule binds to distinct TNF trimers, ultimately forming oligomeric structures that, when they reach a certain size, become insoluble)

[219] Pet. at 54–58, 63.

[220] Ex. 2028 (Bruggemann) at 1359 ("[F]or many therapeutic purposes, an IgG1 antibody might be greatly preferred to other IgG subclasses as it appears to be considerably more effective in mediating both complement-dependent lysis and ADCC.").

IgG fusion protein as an anti-inflammatory treatment,"[221] citing Zettlmeissl as supposedly showing a CD4-IgG1 fusion protein that did not exhibit CDC activity.

But the Zettlmeissl scientists unequivocally state the contrary, both in Zettlmeissl and in a contemporaneous paper.[222] And Zettlmeissl specifically cites concerns over IgG1-based fusions with high-affinity receptors causing autoimmune damage due to CDC activity.[223]

Petitioner also criticizes a declaration submitted by Dr. Arora during examination showing etanercept exhibits unexpectedly low ADCC relative to Humira® and Remicade®. Petitioner attacks those results for not being in a peer-reviewed publication, ignoring that Dr. Arora reported similar results reaching the same conclusion in a refereed journal.[224] And Petitioner cannot seriously dispute the substance of Dr. Arora's findings – the FDA reached the same conclusion, citing, among other things, Dr. Arora's peer-reviewed publication:[225]

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221 Pet. at 39.

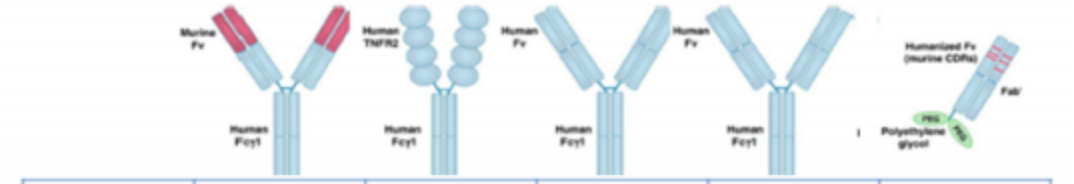
222 Croft-Decl. ¶¶180–189; Zettlmeissl at 348, 352; Ex. 2020 at 42.

223 Croft-Decl. ¶¶171, 189; Zettlmeissl at 352.

224 Pet. at 61–62; Ex. 2026 (Arora-2009) at 124–30.

225 Ex. 2108 (AAC Briefing Document) at 34, n.15 (citing Ex. 2026).

**Figure 12. The Role of Fc in the Anti-TNF-α Class Mechanism(s) of Action**



| | Infliximab | Etanercept | Adalimumab | Golimumab | Cerotlizumab (pegol) |
|---|---|---|---|---|---|
| ADCC | Moderate | Low | Moderate | Moderate | None |
| CDC | Moderate | Low | Moderate | Moderate | None |
| RA | Yes | Yes | Yes | Yes | Yes |

Source: FDA summary of existing literature on the topic of Fc functions of TNF-blockers.[15]

Petitioner's criticisms of Dr. Arora's declaration are plainly unwarranted.

Petitioner also claims that properties such as the binding affinity, neutralization effects, and ADCC/CDC effects of etanercept would not be considered important to its clinical activity. But these are quality attributes the FDA can demand a biosimilar sponsor to evaluate as part of proving their drug is safe and effective.[226] And Coherus itself conducted ADCC and CDC studies to show "CHS-0214 to have highly similar pharmacological activity to Enbrel."[227]

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[226] Ex. 2027 at 20 (ADCC, CDC, "binding," and "neutralization" are "quality attributes").

[227] Ex. 2003 at 12.

### D. Petitioner's Closest Prior Art Assertion is Baseless

Petitioner criticizes Patent Owner for not allegedly comparing the invention to the closest prior art, which Petitioner contends is the "chimeric" antibody in Smith.[228] But Smith does not disclose a single TNFR fusion protein – it describes many different molecules – and its fusion proteins all include a $C_H1$ domain.[229] More directly, etanercept's properties are unexpected and clinically important as measured against any prior art – they are what allow etanercept to halt the progression of RA in the vast majority of patients and have its groundbreaking profile that "revolutionized" the treatment of this disease. Petitioner's contrary arguments all miss the mark.

## VII. CONCLUSION

In view of the above remarks, the Board should decline to institute trial on either of the grounds presented in the petition.

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228 Pet. at 64; *see also id.* at 64–66.

229 *See* Smith at 7:21–28 and *supra* § V.B.1; *Millennium Pharms., Inc. v. Sandoz Inc.*, 862 F.3d 1356, 1368 (Fed. Cir. 2017).

Respectfully submitted,

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## CERTIFICATE OF COMPLIANCE

I hereby certify that the foregoing, Patent Owner's Preliminary Response, contains 13,991 words as measured by the word processing software used to prepare the document, in compliance with 37 C.F.R. § 42.24(d).

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**CERTIFICATE OF SERVICE**

I hereby certify that, on this 15th day of December, 2017, I caused to be served a true and correct copy of the foregoing materials by email on the following counsel:

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